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TI Lysosomal fusion following FcgammaRIIA phagocytosis is mediated by a novel cytoplasmic motif.
AU Worth, Randall G. (1); Kim, Moo-kyung (1); Mayo-Bond, Laura; Todd, Robert F., III; Petty, Howard R.; Schreiber, Alan D. (1)
AB Fusion of phagosomes and lysosomes is a crucial pathway in the destruction of foreign pathogens. Lysosomal fusion in several receptors such as FcgammaRIIB, the mannose-6-phosphate receptor and the LDL receptor is mediated by a di-leucine motif. The sequence(s) responsible for Fcgamma RIIA phagolysosomal fusion is unknown. For example, FcgammaRIIA does not contain a di-leucine motif in its cytoplasmic domain but mediates phagolysosomal fusion. This study was designed to elucidate the mechanism by which FcgammaRIIA mediates lysosomal fusion. We and others have observed that a mutant FcgammaRIIA lacking a cytoplasmic domain is not able to mediate phagocytosis. However, the presence of complement receptor type 3 (CR3) restores phagocytosis, but no lysosomal fusion is observed. Therefore, the cytoplasmic domain of FcgammaRIIA is required for lysosomal fusion. We next disabled the FcgammaRIIA cytoplasmic domain ITAM (immunoreceptor tyrosine-based activation motif) to determine if an intact ITAM is required for lysosomal targeting. Mutation of both tyrosines in the ITAM to phenylalanine abolished phagocytosis. However, co-transfection of CR3 with this ITAM mutant restored phagocytosis and wild-type (WT) levels of lysosomal fusion were observed. After mutation of signaling sequences in the cytoplasmic domain of FcgammaRIIA, we noted that a novel **L-T-L** motif at the C-terminal of the ITAM was responsible for targeting of FcgammaRIIA internalized targets to the lysosomal compartment, but not required for the initial stage(s) of phagocytosis. Mutation of either of the leucine residues individually or in tandem resulted in 70% ($p<0.05$ compared to wt FcgammaRIIA) inhibition of internalized targets to co-localize with lysosomes pre-loaded with fluorescent dextran. Mutation of the threonine alone elicited similar results, thus abolishing 68% ($p<0.05$ compared to wt FcgammaRIIA) of co-localization. However, when the **L-T-L** motif was mutated to A-A-A, lysosomal targeting was abolished similar to that observed with tailless FcgammaRIIA. Therefore, we propose that a novel **L-T-L** motif in the cytoplasmic domain of FcgammaRIIA is responsible for mediating phagolysosomal fusion.
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-	1	ITAM and ltl	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/06/19 16:58
-	1	ITAM and L-T-L	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/06/19 16:58
-	4	fcgammariia	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/06/19 16:58
-	13	ITAM and lysosome	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/06/19 17:00
-	136	ITAM and fusion	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/06/19 17:02